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PART XXIV
SKIN DISEASES

Frank Parker

530 INTRODUCTION

An understanding of how the skin functions in health and disease is relevant to every physician for several reasons: First, the skin is the interface with our environment and serves many functions crucial to survival, such as protection against the elements and thermoregulation. Second, the psychologic role the skin and its appendages, the hair and nails, play in our appearance cannot be overestimated. Third, skin problems are exceedingly common, as some 30 per cent of Americans have dermatologic conditions requiring a physician's care. Ten common skin problems constitute 76 per cent of the burden of skin disease as established by population survey (Table 530–1). Fourth, the skin can be readily examined and biopsied and frequently provides evidence of internal disease. The trained examiner recognizes certain apparently insignificant skin findings as subtle signs of life-threatening disease.

Chapter 531 reviews the functions subserved by the skin and the local variations in skin structures which help to explain the localization of certain disease processes to specific areas. Chapter 532 discusses the examination of the skin and presents an approach to diagnosing skin diseases based upon clinical morphology. Nine major disease groupings are described, and the common dermatologic conditions and their etiologies are discussed (Ch. 534). Chapter 533 contains a guide to general principles of therapy. Chapter 534 describes skin diseases of general medical importance as well as specific therapy for each disease.

TABLE 530–1. PREVALENCE OF COMMON DERMATOLOGIC DISEASE IN THE UNITED STATES*

	Rate per 1000	Numbers (in 1000's)
Fungus infections	81.1	15,733
Tinea pedis	38.7	7509
Tinea ungulum	21.8	4232
Tinea versicolor	8.4	1623
Tinea cruris	6.7	1301
Acne vulgaris	68.1	13,217
Cystic acne	1.9	375
Acne scars	1.7	321
Seborrheic dermatitis	28.2	5476
Verruca vulgaris	8.5	1684
Folliculitis	8.0	1553
Atopic dermatitis	6.9	1332
Lichen simplex chronicus	4.5	882
Hand eczema	1.6	311
Dyshidrotic eczema	2.1	405
Psoriasis	5.5	1070
Vitiligo	4.9	957
Herpes simplex	4.2	824

*Persons 1 to 74 years of age—noninstitutionalized.
Reprinted from the chapter by Dr. Marie-Louise Johnson in the 17th edition of the Cecil Textbook of Medicine, with her permission.

Callen JP: Cutaneous Aspects of Internal Disease. Chicago, Year Book Medical Publisher, 1981. *Discussions of skin disorders that confront the clinician which have underlying systemic disorders. Discussion of the pathogenesis of these disorders is provided by a number of contributing authorities.*

Fitzpatrick TB, Eisen AZ, Wolff K, et al.: Dermatology in General Medicine. New York, McGraw-Hill Book Company, 1987. *A detailed and well-illustrated textbook covering all aspects of dermatology. Two volumes.*

Hurwitz SH: Clinical Pediatric Dermatology. Philadelphia, W. B. Saunders Company, 1981. *A well-written and well-illustrated book of dermatology of children and adolescents.*

Lookingbill DP, Marks JG Principles of Dermatology. Philadelphia, W. B. Saunders Company, 1985. *A concise, well-illustrated textbook covering major topics in general dermatology.*

Moschella SL, Pillsbury DM, Hurley HJ: Dermatology. Philadelphia, W. B. Saunders Company, 1975. *A useful textbook of dermatology in two volumes.*

Rook A, Wilkinson DS, Ebling FJG, et al.: Textbook of Dermatology. Oxford, Blackwell Scientific Publication, 1986. *This three-volume multi-authored text covers every aspect of dermatology in great detail. It is well written and referenced.*

531 THE STRUCTURE AND FUNCTION OF SKIN

The skin serves a variety of functions crucial to survival and health. In general, the functions may be correlated with specific properties of epidermal or dermal regions. The epidermis differentiates to form anucleate cornified cells that act as a relatively impermeable protective barrier to the outward loss of body fluids and the inward penetration of various substances and microorganisms. These lamellae of cornified surface cells together with the brown pigment melanin also play an important role in protecting against the carcinogenic effects of ultraviolet radiation. Two components of the dermis, the unique circulatory system and the specialized cutaneous appendages, the sweat glands, play a vital role in the body's thermoregulation. Finally, the skin is important immunologically. Both the epidermis (Langerhans' cells) and dermis (epidermodermal junction structures) are sites at which a number of immunologic reactions occur that can give rise to unique inflammatory skin diseases.

ANATOMIC CONSIDERATIONS

The skin is composed of two mutually dependent layers: the outer *epidermis* and inner *dermis*, both cushioned on the fat-containing subcutaneous tissue, the *panniculus adiposus* (Figs. 531–1 and 531–2).

EPIDERMIS. The stratified cellular epidermis contains two main zones of cells (keratinocytes), an inner region of viable cells, the *stratum germinativum*, and an outer layer of anucleate cells known as the *stratum corneum*, or horny layer. Three strata of cells are recognized in the germinativum: the *basal*, *spinous*, and *granular* layers, each representing progressive stages of differentiation and keratinization of the epidermal cells as they evolve into the dead, tightly packed stratum corneum cells on the skin surface.

tivities of the skin are under hormonal regulation to the ctent that the skin is recognized as an important hormone id organ. Indeed, not only do sebaceous glands and certain air follicles respond readily to androgens, but they are apable of many diverse steroid transformations, as described bove.

Dihydrotestosterone causes sebaceous glands to enlarge at uberty, the growth of certain hair (male sexual hair of the eard, chest, upper pubic triangle, nose, and ears), and the rowth and development of the external genitalia. Antiandrogens, drugs that block the conversion of testosterone to DHT, lo this by competitively inhibiting either 5 alpha-reductase or he cytosol receptor protein for DHT. Drugs such as cimetidine nd spironolactone have antiandrogenic activity and have een used to treat acne and hirsutism. In addition, thyroid ormones can regulate hair growth and alter the texture of he skin (fine, sparse hair and smooth, soft skin in hyperthyroidism; coarse hair and cool, rough, thick skin in hypothyroidism). Further, hormones affect melanin pigment formation, melanocyte stimulating hormone, and estrogen stimulating skin pigmentation.

THE SKIN AS AN IMMUNOLOGIC ORGAN. The epidermis and the dermoepidermal junctional area serve as active participants in immunologic reactions. The skin is composed of immunologically important cells including keratinocytes, Langerhans' cells, and melanocytes as well as immunologic structures such as the lamina lucida and basal lamina that are involved in a variety of bullous reactions of the skin.

Epidermal Immunologically Important Cells. Perhaps the most important immunologic cell in the epidermis is the Langerhans' cell, comprising 2 to 5 per cent of the total epidermal cell population. Langerhans' cells play a role in a number of immunologic reactions, including macrophage–T cell interaction, T and B lymphocyte interactions, graft versus host (GVH) reactions, and skin graft rejection. The Langerhans' cell synthesizes and expresses Ia antigens (Class II antigens, immune response gene–associated antigens) that are crucial in processing and presenting allergens to sensitized T lymphocytes critical in the elicitation of delayed hypersensitivity contact dermatitis. Lymphokines, made by the Langerhans' cells during these immunologic reactions, augment and enhance these processes and also contribute to the accompanying inflammatory response.

Keratinocytes also play a role in immunologic responses by expressing Ia antigens on their surfaces in such conditions as GVH reaction, mycosis fungoides, allergic contact dermatitis, lichen planus, and tuberculoid leprosy. In these conditions the keratinocytes make lymphokines, particularly interleukin 1 (ETAF, epidermal cell thymocyte factor), which provides a second signal supplementing macrophages (Langerhans' cells) in mitogen- and antigen-induced T cell activation. In addition, epidermal cells make other cytokines such as prostaglandin-E2 and leukotrienes that participate in inflammatory reactions in the skin. Keratinocytes are the immunologic target in the pemphigus group of diseases where circulating autoantibodies against intercellular antigen of the epidermis and mucous membrane epithelium initiate intraepidermal acantholytic bullae.

The Dermoepidermal Junction as an Immunologic Structure. A variety of inflammatory diseases often characterized by bullous reactions seem to be mediated by immunoreactants, including IgG, IgA, and IgM, and complement deposition along the dermoepidermal junctional area. The anatomic site of blister formation correlates with the position of deposition of these immunoreactants. The antigens in several diseases have been isolated and partially characterized. The use of immunofluorescent techniques at the light microscopic and especially the ultrastructural level has been very helpful in more precisely diagnosing these bullous conditions. These are summarized in Table 531–3, along with immunofluorescent skin findings in connective tissue diseases.

INFLAMMATORY REACTIONS IN THE SKIN AND WOUND HEALING. Cutaneous inflammation reflects the sum of the effects of biologic products of cells (mast cells,

TABLE 531–3. IMMUNOFLUORESCENT CUTANEOUS FINDINGS IN IMMUNOLOGICALLY MEDIATED SKIN DISEASE

Diseases	Biopsy Findings of Direct Immunofluorescence Immunoreactants (DII)	Ultrastructural Localization of Immunoreactants	Site of Blister Formation on Routine Light Microscopic Pathology	Serum Findings: Indirect Immunofluorescence (IIF)
Bullous Diseases				
Pemphigus (all forms)	Deposits of IgG intercellular areas between keratinocytes	Between keratinocytes	Suprabasilar in pemphigus vulgaris; substratum corneum in pemphigus foliaceus	IgG antibodies to intercellular areas of keratinocytes in 90% of patients
Bullous pemphigoid	IgG and/or complement (C) in basement membrane zone (BMZ)	Lamina lucida and hemidesmosomes—upper part lucida and sub-basal cells	Subepidermal	IgG Ab to BMZ in 70%
Cicatricial pemphigoid	IgG and/or C in BMZ	Lamina lucida	Subepidermal	IgG antibodies BMZ in 10%
Herpes gestationis	Complement in BMZ—occasionally IgG	Lamina lucida—close to lamina densa	Subepidermal—sub-basal cell—above lamina densa	IgG antibodies BMZ in 20% (HG factor in 25%)
Dermatitis herpetiformis	IgA and C in dermal papillae (granular deposits)	Granular IgA associated with microfibril bundles in dermal papilla	Subepidermal in dermal papillae—papillar dermal microabscesses	No circulating antibodies
Epidermolysis bullosa acquisita	IgG in BMZ	Sublamina densa amorphous granular deposits	Subepidermal	No circulating antibodies
Linear IgA bullous dermatosis in childhood	IgA and complement in linear deposition in BMZ	—	Subepidermal	No circulating antibodies
Connective Tissue Diseases				
Bullous SLE	IgG, IgM, and complement in BMZ in involved and normal skin—linear homogeneous	Just beneath lamina densa (basal lamina)	Subepidermal	No circulating antibodies to BMZ; ANA found in 90%
Discoid LE	IgG, other Ig, and C in lesional skin at BMZ	—	—	No circulating antibodies to BMZ, ANA titers normal
Systemic LE	IgG band at BMZ in normal skin (over 90% in sun-exposed areas)	—	—	Elevated ANA titers
Systemic sclerosis	Nucleolar IgG	—	Epidermal thinning and increased dermal collagen	ANA, speckled, 85%; centromere + in CREST syndrome
MCTD	IgG/IgM in BMZ in some patients; nuclear IgG in epidermis	—	—	Speckled ANA and ENA (extractable nuclear antigens)
Dermatomyositis	Negative	—	—	ANA often normal range

infiltrating neutrophils, monocytes/macrophages, lymphocytes) as well as the effects of the products of the complement system, membrane-derived arachidonic acid metabolic pathways (prostaglandins and leukotrienes) and the Hageman factor–dependent pathways of coagulation, fibrinolysis, and kinin generation. Early phases of wound healing also encompass many of these reactions.

Cutaneous Inflammation. A variety of pathophysiologic reactions initiate inflammation, including infectious, immunologic, and toxic processes that affect the epidermis or dermis, or both. Mast cells in the skin not only function as the sentinel cells in immediate-type hypersensitivity reactions but also as major effector cells in inflammatory reactions releasing (1) histamine, prostaglandin D2, and leukotrienes, which cause vascular dilatation and increased permeability, redness, swelling, pain, and itch; (2) chemotactic factors for eosinophils and neutrophils; (3) proteases that interact with the complement, kinin, and fibrinolytic pathways; and (4) heparin, which may play a role in local angiogenesis. Degranulation of mast cells occurs in response to various antigens that cross-link IgE on the mast cell surface (immediate hypersensitivity reactions), to by-products of complement activation C3a and C5a (as occurs in leukocytoclastic vasculitides), as well as to radiocontrast media, aspirin, insect venom, and various physical stimuli. Circulating peripheral blood cells infiltrate local tissue sites in response to chemotactic factors released by mast cells and other infiltrating cells. Basophils release histamine and chemotactic substances, such as those involved in allergic contact reactions, bullous pemphigoid, erythema multiforme, and inflammatory responses. Neutrophils release myeloperoxidase, acid hydrolases, and neutral proteases that are active against microbes and cause tissue destruction (dermatitis herpetiformis, psoriasis, leukocytoclastic vasculitis, and bacterial infections of the skin). Eosinophils release major basic protein and peroxidase (allergic drug reactions in the skin, bullous pemphigoid). Lymphocytes release lymphokines that modulate immunologic and inflammatory responses (lichen planus, lupus erythematosus, allergic contact dermatitis, tuberculoid leprosy). Monocytes and macrophages engulf foreign proteins and microorganisms (granulomatous reactions in the skin such as sarcoidosis, deep fungus and acid–fast bacilli infections, and cutaneous foreign body responses). In addition, both classic and alternate complement pathways release products that induce mast cell degranulation and induce inflammation. (The activation of the system seems to play a role in inflammatory reactions in hereditary complement deficiencies causing lupus erythematosus–like syndromes or pyodermas, as well as necrotizing vasculitis.)

Wound Healing in the Skin. Healing proceeds temporally in three phases: substrate, proliferative, and remodeling. The initial substrate phase, encompassing the first three to four days after wounding, is so named because the cellular and other interactions lead to preparation for subsequent events. During this phase vascular and inflammatory components prevail (vascular clotting in the severed vessels; leukocyte and macrophage chemotaxis into the area to ingest bacteria, debride the wound, and degrade collagen). The proliferative phase (10 to 14 days after wounding) results in regeneration of epidermis, neoangiogenesis, and proliferation of fibroblasts with increased collagen synthesis and closure of the skin defect. The final remodeling phase takes place over 6 to 12 months, during which time a more stable form of collagen is laid down to form a scar of progressively increasing tensile strength. In some instances so much collagen is deposited in the healing wound that an elevated *hypertrophic scar* (red, raised scar within the boundaries of the original wound) or keloid (scar tissue extending beyond the boundaries of original injury into surrounding normal tissue) is produced. Keloids, which occur most commonly over the anterior chest, upper back, and deltoid regions, rarely regress, and they recur after excision. Fibroblasts from keloid areas synthesize collagen at significantly greater rates than normal skin, even in tissue culture.

THE COSMETIC IMPORTANCE OF SKIN. With age virtually all the structures and functions of the skin change. Environmental insults, especially chronic sun exposure, cause far greater destruction of the skin than time itself. Sun exposure over a lifetime, especially in fair-skinned, easily sunburned individuals, accelerates the aging process, resulting in thin, wrinkled, skin in exposed areas. The major age changes in gross appearance of skin include roughness, wrinkling, laxity, uneven pigmentation, and a variety of benign and malignant proliferative lesions.

Changes with aging at the structural, physiologic, and biochemical level are as follows: (1) A decrease in epidermal turnover rate of approximately 50 per cent occurs between the third and seventh decades. Concurrent loss of dermal elastic and collagen fibers accounts for the paper-thin, transparent quality of aged skin and the easy rupture of dermal vessels. Further, with age there is increasing cross-linkage of collagen and elastin, making the dermis more rigid and therefore less able to withstand shearing forces. Aged skin, when "tented up," only slowly returns to its original form, whereas young skin readily snaps back. (2) Sun-damaged aged skin shows microscopic collagen damage. Dermal collagen is replaced by amorphous basophilic staining material. This condition, termed *elastosis*, results in deep wrinkling and furrowing, especially over the face and back of the neck, and yellow papules and nodules in a reticular pattern on the face. (3) Decreases in the number of functioning sebaceous and sweat glands contribute to the dryness of aged skin and to impaired thermoregulation in aged persons. (4) Reduction in the vascular network in the skin surrounding hair bulbs and eccrine and sebaceous glands may be responsible for the atrophy of these appendages with age. (5) A 50 per cent reduction in the number of Langerhans' cells may account in part for the age-associated decrease in immune responsiveness and allergic contact dermatitis reactions in the elderly. (6) Loss of enzymatically active melanocytes (10 to 20 per cent per decade) causes irregular pigmentation of the skin and graying of the hair. (7) Gradual reduction occurs in the number of body hairs, especially in the scalp, axillary, and pubic regions (related in part to decreased androgen production). (8) Linear growth of nails also decreases by 30 to 50 per cent between early and late adulthood. Often nails become brittle and thickened. (9) A number of proliferative growths are associated with aging skin, including skin tags (acrochordon), cherry angiomata, seborrheic keratosis, lentigenes, and sebaceous hyperplasia.

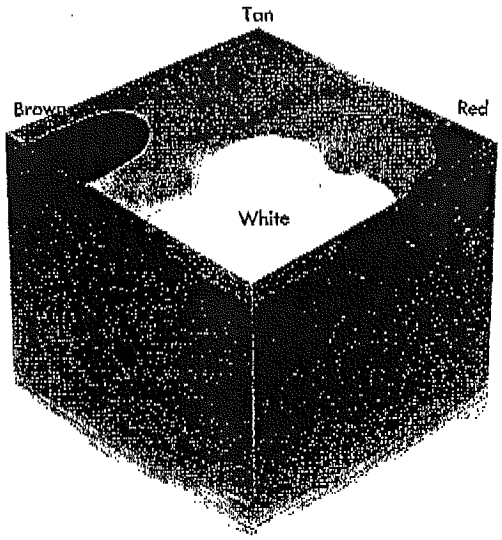
532 EXAMINATION OF THE SKIN AND AN APPROACH TO DIAGNOSING SKIN DISEASES

General considerations in history taking and physical examination:

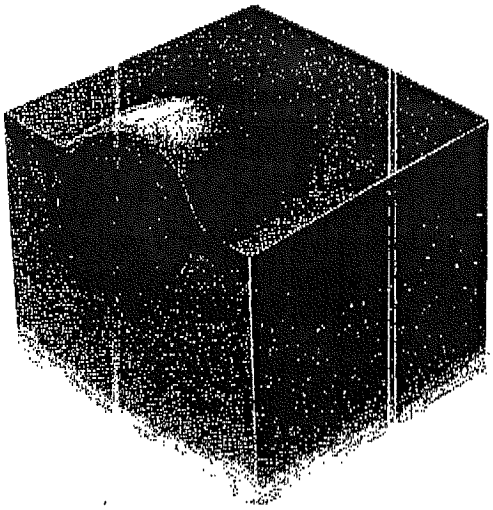
THE DERMATOLOGIC HISTORY

A proper history includes the following: where the patient's skin condition first appeared; what it looked like and what symptoms, if any, were associated with it initially; how the skin disease progressed and changed and what has been done to treat the condition by the patient or by other physicians).

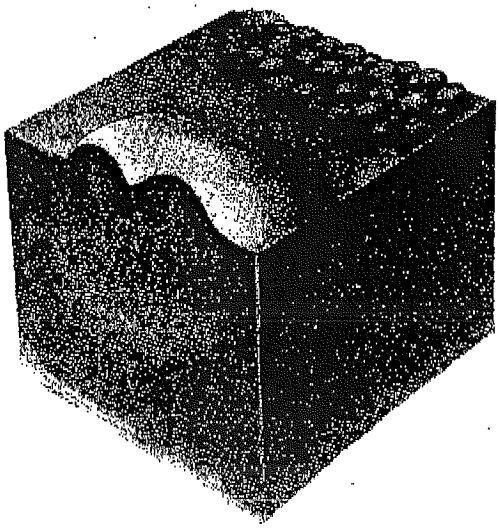
A careful review of the systemic medications (both proprie-



MACULE
A circumscribed color change

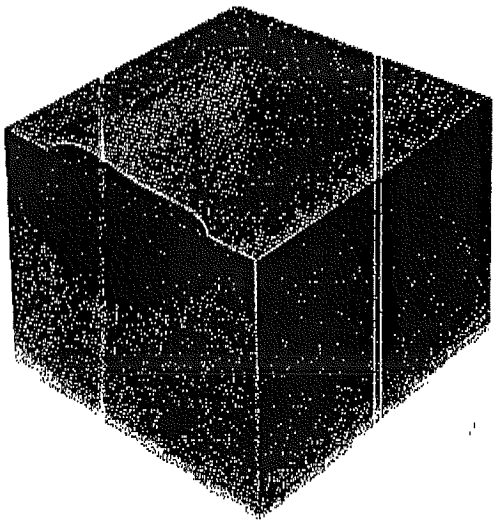


CYST
Semi-solid sac
Resilient



PAPULE
A solid elevation 1 cm or less skin colored or not

PLAQUE
Raised, circumscribed, extensive



WHEAL
Evanescent
Edematous
Erythematous

FIGURE 532–1. Lesions of the skin. (From the 17th edition of the Cecil Textbook of Medicine, with the permission of Dr. Marie-Louise Johnson.)

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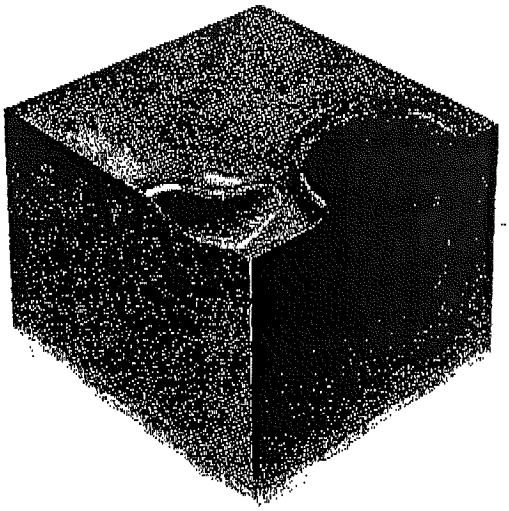
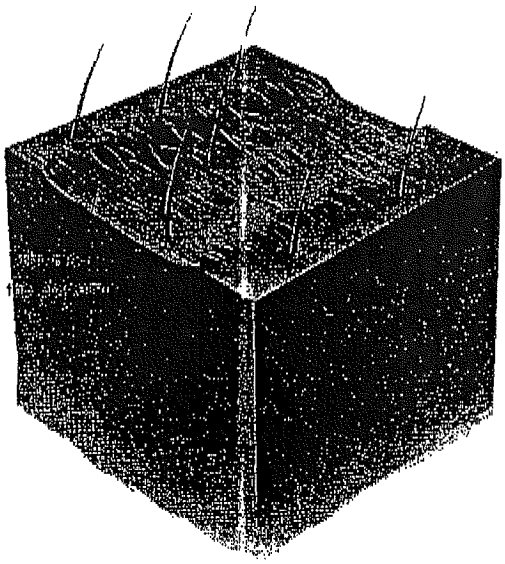
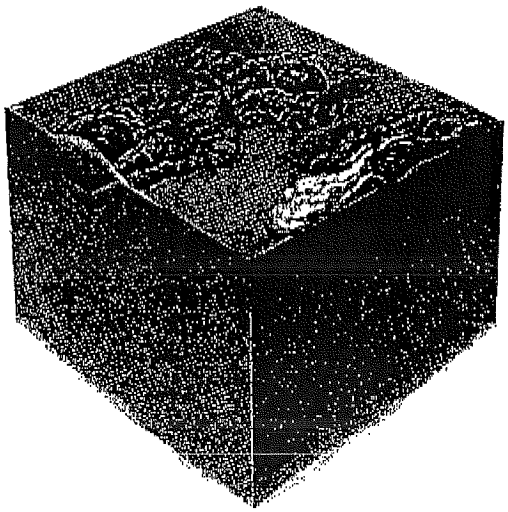


EROSION
Superficial denudation

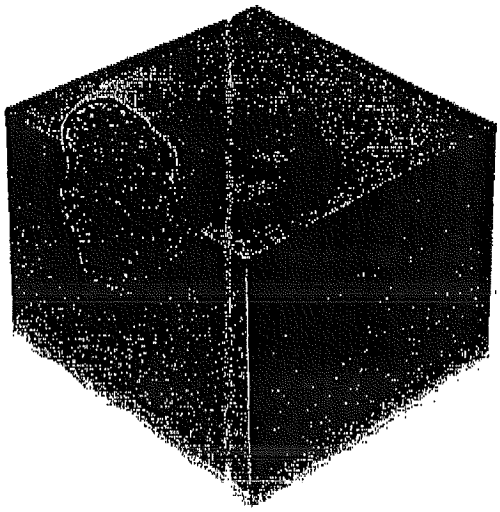
ULCER
Defect penetrates dermis



ATROPHY



CRUST
Coagulated blood elements



PUSTULE
Fluid-filled sac with neutrophils

FIGURE 532–1. *Continued.*

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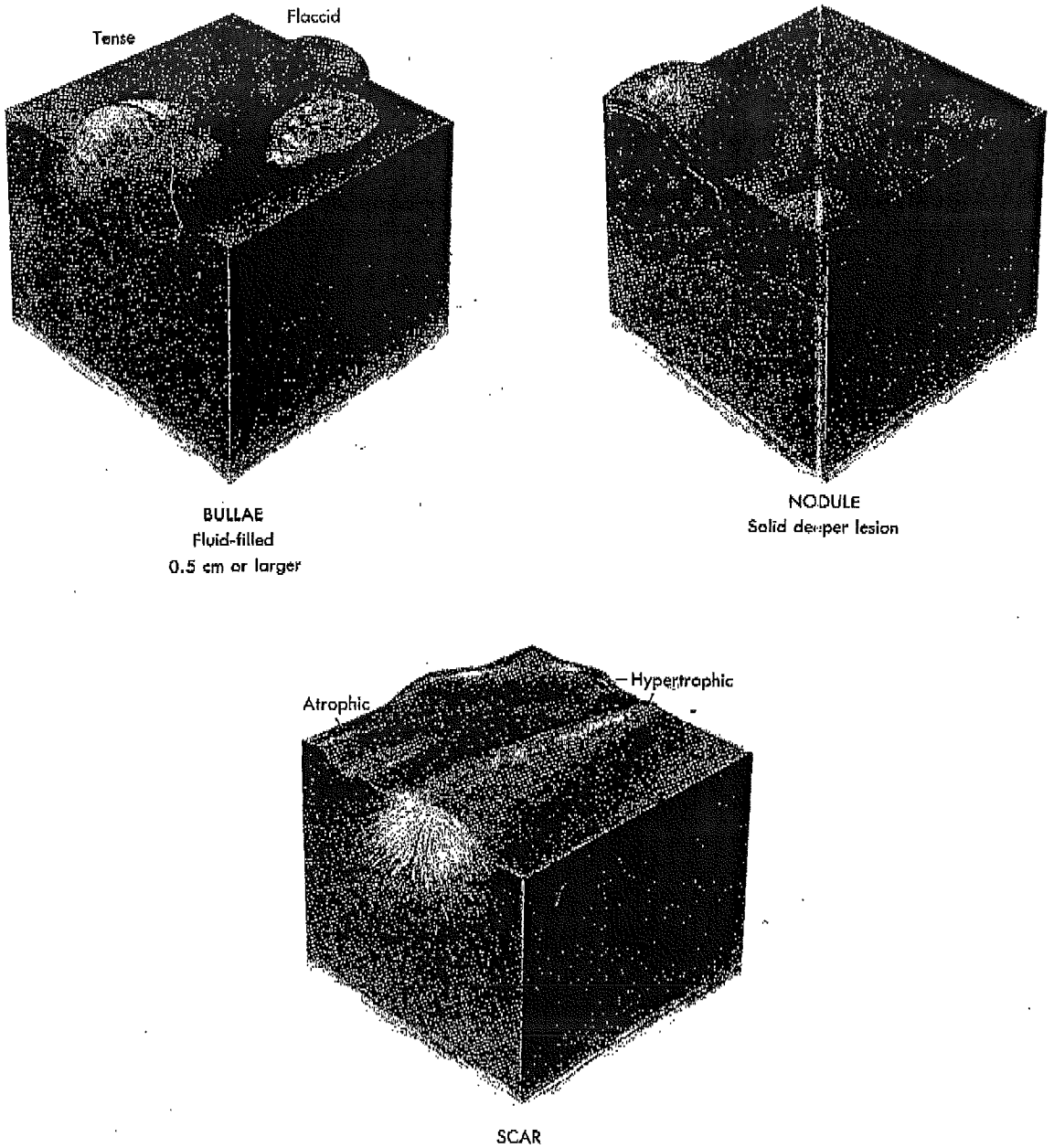

FIGURE 532–1. *Continued.*

esion). Iris lesions are seen in erythema multiforme. *Arciform* esions form partial circles or arcs and may be seen in lermatophyte infections. *Polycyclic* patterns evolve when nuerous annular lesions enlarge and run together. *Serpiginous* snakelike, undulating, linear) patterns are seen in creeping ruptions and in psoriasis. *Herpetiform* refers to a grouping of esions such as occurs in herpes simplex or dermatitis herpetiformis.

Other physical features are important in diagnosing skin liseases: Dry, lichenified lesions suggest a chronic state of a lisease, whereas wet, weeping, macerated lesions suggest icute reactions. Abscesses are soft and fluctuant, whereas iodules are usually firm. Redness caused by dilatation of superficial blood vessels will blanch with pressure, whereas erythema caused by extravasated blood as occurs in petechiae and purpuric lesions will not blanch. Hues of brown to black usually indicate melanin, although some drugs (e.g., tetracycline) cause brown-black pigmentation in the skin. The variation in color from melanin is related to the depth of the pigment in the skin—the deeper the pigment the more blue-black the color.

DIAGNOSTIC TESTS AND AIDS IN EXAMINATION OF THE SKIN

Certain technical, clinical, and laboratory aids and procedures, when combined with the history and physical examination, are indispensable in arriving at the correct diagnosis.

VISUAL AIDS. ***Magnification.*** Certain diagnostic findings are revealed by magnification of the skin lesions, for example,

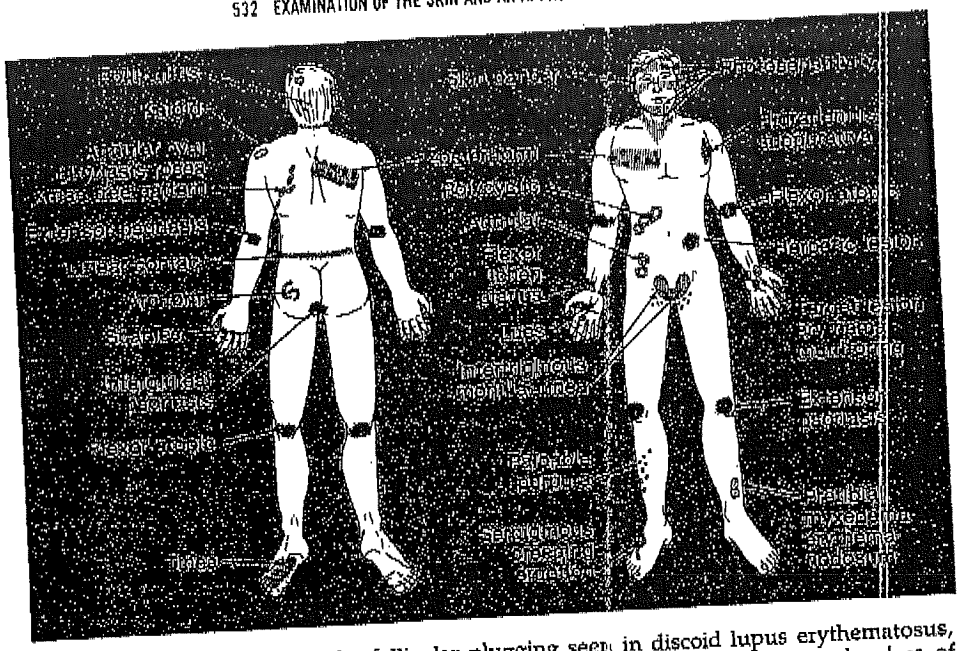

FIGURE 532–2. Configurational and regional diagnostic aids for the diagnosis of primary and secondary skin lesions.

TABLE 532–1. MAJOR GROUPS OF DERMATOLOGIC DISEASES BASED ON THE CLINICAL MORPHOLOGY OF THE SKIN CONDITION

Group	Clinical Morphology	Examples of Diseases in the Group
Eczema or dermatitis	Macules (erythema), papules, vesicles, lichenification, fine scaling, excoriations, crusting	Contact dermatitis, atopic dermatitis, stasis dermatitis, photodermatitis, scabies, dermatophytoses, exfoliative dermatitis, candidiasis
Maculopapular eruptions	Macules, erythema, papules	Viral exanthems, drug reactions, verruca vulgaris, Kawasaki's disease, vasculitic and purpuric eruptions
Papulosquamous dermatoses	Papules, plaques, erythema with unique scales	Psoriasis, Reiter's syndrome, pityriasis rosea, lichen planus, seborrheic dermatitis, ichthyosis, secondary syphilis, mycosis fungoides
Vesiculobullous diseases	Vesicles, bullae, erythema	Herpes simplex and zoster, hand-foot-and-mouth disease, insect bites, bullous impetigo, scalded skin syndrome, pemphigus, pemphigoid, dermatitis herpetiformis, porphyria cutanea tarda, erythema multiforme
Pustular diseases	Pustules, cysts, erythema	Acne vulgaris and rosacea, pustular psoriasis, folliculitis, gonococcemia
Urticaria, persistent figurate erythemas, cellulitis	Wheals and figurate, raised erythema, scaling	Urticaria, erythema annulare centrifugum, erysipelas, necrotizing fasciitis
Nodular lesions	Nodules and tumors, some associated with erosions and ulceration	Benign and malignant tumors—basal cell cancer, squamous cell cancer, rheumatoid nodules, xanthomas
Telangiectasias, atrophic, scarring, ulcerative diseases	Atrophic, sclerotic telangiectasias and ulcerative changes	Connective tissue diseases, radiation dermatitis, lichen sclerosus et atrophicus, vascular insufficiency (arterial and venous), pyoderma gangrenosum
Hyper- and hypomelanosis	Increased and decreased melanin deposition in skin	Acanthosis nigricans, café au lait spots, vitiligo, tuberous sclerosis, xeroderma pigmentosum, chloasma, freckles

the follicular plugging seen in discoid lupus erythematosus, or fine telangiectasias in the pearly, opalescent borders of basal cell cancers.

Transillumination. Oblique lighting in a darkened room can be useful in detecting slight degrees of elevation or depression of lesions as well as fine wrinkling or atrophy of the epidermis. In addition, the application of a penlight directly to nodular lesions in a dark room may give clues as to the density and make-up of such lesions. Cystic lesions allow transmission of some light, whereas nodules composed of cellular infiltrates do not.

Diascopy. Firm pressure with a microscope slide against skin lesions differentiates erythema of capillary dilatation from that of extravasated blood. Sarcoidosis, tuberculosis, and other granulomatous inflammatory reactions in the skin are suggested if diascopy of the lesions shows a characteristic "apple-jelly" or glassy, fawn-colored appearance.

Long-wave Ultraviolet or Wood's Light Examination. Long-wave ultraviolet light (UVA) (360 nm) is useful in evaluating several conditions of the skin. Wood's light is of great help in estimating subtle variations in pigmentation. It exaggerates the differences in the degree of pigmentation when the skin is examined with the lamp in a dark room. Melanin is a universal absorber of UV light, so decreased melanin shows more reflection (light color) and increased melanin less reflection (darker color). Pigment in the epidermis is exaggerated with UVA light, but that in the dermis is not, so a reasonable guess as to the site of melanin in the skin can be made. Wood's light may be the only means of recognizing the hypomelanotic ash leaf–shaped macules in tuberous sclerosis. The extent of vitiligo and melanotic nevi (which appear darker than surrounding normal skin) can also be determined. Some superficial fungal infections of the scalp fluoresce blue-green; erythrasma, a superficial intertriginous bacterial infection that produces a porphyrin, fluoresces a brilliant coral red; *Pseudomonas* infections may give off yellow-green color under a Wood's light.

CLINICAL TESTS. *Patch Tests.* Patch testing is used to validate a diagnosis of allergic contact sensitization and to identify the causative allergen. Since the entire skin of sensitized humans is allergic, the test reproduces the dermatitis in one small area where the allergen is applied, usually on the back. The suspected allergen is applied to the skin, occluded, and left in place 48 hours. A positive test reproduces an eczematous response at the test site from 48 hours up to a week after the test. The latter is a delayed hypersensitivity

TABLE 534–1. ECZEMATOUS DERMATITIS SKIN ERUPTIONS

Clinical Type	Etiology or Suspected Cause	Distinctive Diagnostic Findings
Eczemas with Known Causes		
Contact dermatitis		
Irritant contact	Chemical agents that have direct toxic effects on skin	Contact precedes rash by hours to days
Allergic contact	Chemical agents that elicit type IV delayed hypersensitivity reaction on skin	Contact precedes rash by two or more days; in both instances site and configuration of eczema reaction conform to site of contact with exogenous substances (plants, medicaments, cosmetics, metals); patch tests
Photodermatitis	Ultraviolet light exposure plus topical or systemic substances induce type IV delayed hypersensitivity	Eczematous reaction in sun-exposed areas of skin with sharp "cut off" borders, i.e., face, ears, V of neck, dorsum of hands, extensor surfaces of arms
Eczematous drug-induced reaction	Drugs such as penicillin taken internally	Generalized eczema reaction evolves after taking medications (usually 10 or more days after first beginning drug; sooner if previously exposed) and clears with stopping drug
Dermatophyte and *Candida* eczematous reactions	Dermatophytes and *Candida* induce eczematous inflammatory reaction	Dermatophyte or yeast found in scales or exudate
Infectious eczematoid dermatitis	Products from draining infected skin areas induce eczema reaction—linear infections, leg ulcers	Occurs near site of infection or other draining lesion; clears with treatment of infection
Dermatophytid	Hypersensitivity reaction occurring on distant areas of skin in response to products from fungal infection of other areas of skin	Often vesicular eruption of palms or fingers with dermatophyte infection of feet
Autosensitization	Hypersensitivity reaction to cutaneous or bacterial antigens released from area acute dermatitis	Generalized dermatitis following localized acute dermatitis
Xerotic eczema or eczema craquelé	Dry skin or xerosis	Can lead to redness and fissuring of skin that appear as cracks in dried mud
Eczemas with Unknown or Unclear Etiologies		
Atopic eczema	Hereditary disposition in association with familial tendency for asthma and allergic rhinitis	Eczematous reaction often localized to face, neck, antecubital, and popliteal areas
Stasis dermatitis	Chronic venous insufficiency	Associated with varicosities, leg edema, hyperpigmentation, and ulcers
Lichen simplex chronicus (neurodermatitis)	Repeated scratching leads to eczema	Lichenified patches in areas within reach of fingers (nape of neck, lower legs)
Nummular eczema	Dry skin, underlying infections; sometimes seen in atopic dermatitis	Coin-shaped patches on extensor areas of extremities and trunk
Seborrheic dermatitis	Occurs in areas of high concentrations of sebaceous glands; may be related to intrinsic yeast in skin (*Pityrosporon ovale*)	Inflammatory, yellow, greasy, scaling patches on scalp, retroauricular, eyebrows, nasolabial fold, and presternal areas
Dyshidrotic eczema	Emotional stress—unrelated to disturbances in sweating	Pruritic vesicles on palms, soles
Nonspecific eczematous dermatitis	No obvious cause—diagnosis of exclusion after above eczemas ruled out	Acute and chronic eczema patches anywhere on body; severe itching

sumac as well as in cashews, mangos, and ginko trees), paraphenylenediamine (a substance in hair dyes which cross-reacts with benzocaine and hydrochlorothiazide), nickel, mercaptobenzothiazol and thiuram (components in rubber), and ethylenediamine (a preservative in many medications and also found in industrial dyes and insecticides). Other common sources of contactants include topical medications (neomycin, anesthetics such as benzocaine, topical antihistamines), preservatives (ethylenediamine, merthiolate, parabens), vehicles (propylene glycol), and cosmetics (fragrances, preservatives, paraphenylenediamines). It is obvious that a detailed history of the patient's occupation, hobbies, habits, clothing, cosmetics, and medications applied to the skin is necessary to find the contactant. Careful detective work on the part of the physician and the patient will often bring to light the etiologic factor. One must not overlook the possibility that a topical medicine is perpetuating or exacerbating a pre-existing dermatitis.

There is no standard testing method available for diagnosing irritant contact dermatitis. For allergic contact eczema, the causative agent can be identified by patch tests, but these must be properly performed and interpreted by trained dermatologists.

Therapy of contact dermatitis is avoidance of the irritant or allergen if possible. This may require a change in lifestyle or occupation. Sometimes protective clothing is curative. Barrier creams are of little benefit. Acute, severe generalized contact dermatitis is treated with a short (10- to 14-day) course of systemic steroids and wet dressings or baths. Milder eczematous reactions respond to topical steroids and systemic antihistamines.

PHOTODERMATITIS. A variety of skin reactions, termed photosensitivity reactions, may occur in response to exposure to ultraviolet light. Some appear as eczematous reactions, so-called photoallergic dermatitis, which may occur in response to topical as well as systemic substances in the presence of UV light. The distribution of the eczematous eruption in light-exposed areas is an important feature in the differential diagnosis, with the cheeks nose, forehead, and tips of ears as sites of predilection. The backs of hands and forearms are also frequently involved and, of course, the history of exposure to UV light prior to the onset of the reaction is important in identifying light sensitivity (see Fig. 532–2).

Photoallergic dermatitis is immunologic. Absorption of a specific wavelength of ultraviolet light by a topical substance or a systemic drug (which is deposited in the skin from the subcutaneous circulation) causes chemical conversion of the substance or drug to a hapten that binds cutaneous proteins to become a complete antigen capable of eliciting a type IV delayed hypersensitivity reaction similar to an allergic contact dermatitis reaction. Photoallergic reactions appear only where the UV light hits the skin even though the systemic drug or topical photoallergen is present in the skin all over the body; i.e., the reaction depends on UV light hitting the skin with the allergen in it. Long wavelength UVA light is usually responsible for these reactions. UVA light penetrates window glass (UVB light is blocked by glass), so the reaction often occurs even though the patient remains indoors. Such drugs as thiazides and phenothiazines can cause photoeczematous reactions; a number of topically applied substances, such as methylcoumarin, musk ambrette, halogenated salicylanilids, and topical sunscreening agents, can cause a similar reaction. Photopatch testing can identify substances in materials causing these reactions. Avoidance of the offending material is often curative. Oral or topical steroids will relieve the inflammatory reaction.

TABLE 534–6. VESICULOBULLOUS DISEASES

Location of Blister in Skin	Etiology if Known	Important Physical Findings	Other Facts of Note in History or Laboratory Results
Intraepidermal Blisters			
Bacterial infectious processes			
Bullous impetigo (subcorneal)	Staph toxin	Large, fragile, clear or cloudy bullae that break to leave honey-yellow crusts on face, neck, extremities; erythematous areas that slough as superficial blisters	An initial site may be followed by multiple pruritic autoinoculated sites
Staph scalded skin syndrome—upper epidermal blisters	Staph toxin		
Viral infections			
Herpes simplex, eczema vaccination, herpes zoster varicella (ballooning degeneration)	Direct cell damage	Grouped umbilicated vesicles on erythematous base anywhere on body; diffuse umbilicated vesicles in sites of atopic eczema; unilateral grouped umbilicated, clear or hemorrhagic vesicles in dermatomal distribution	Frequently recurrent; respond to acyclovir
Insect bites	Insect toxins or proteases, delayed hypersensitivity	Papules, bullae—pruritic	Associated with radicular pain and hypesthesia of involved dermatome; respond to acyclovir
Eczema—acute contact (spongiosis)	Type IV hypersensitivity or irritant	Vesiculobullous lesions on red base; often form unusual patterns of contact with substances	
Autoimmune diseases			
a) Pemphigus vulgaris and vegetans (suprabasilar split)	a) Autoimmune interepidermal cell IgG and C3	a) Superficial, flaccid bullae that readily rupture, leaving nonhealing erosions over the body that can cause death; Nikolsky's sign prominent	a) 100% of patients develop mucous membrane blisters, erosions
b) Pemphigus foliaceus and erythematosus (subcorneal split)	b) Autoimmune IgG and/or C3 between cells in upper epidermis	b) Superficial blisters crusting, oozing over scalp and face in seborrhea distribution or butterfly-like rash	b) Seldom see mucous membrane involvement
c) Hailey-Hailey disease (suprabasilar split)	c) Genetically inherited—dominant	c) Superficial erosive blisters, vesicles, pustules in flexural areas of body	c) No mouth lesions
Subepidermal Blisters			
Autoimmune or immunologic			
Bullous pemphigoid	C3 in lamina lucida	Tense bullae on normal or erythematous skin	
Herpes gestationis	C3 in basement membrane zone	Erythematous plaques, tense vesicles, and pruritic bullae that evolve first on abdomen and then on extremities; often polycyclic	Develops during 2nd or 3rd trimester of pregnancy—clears with delivery; increased fetal wastage
Erythema multiforme	Hypersensitivity reaction in blood vessels of dermis to number of antigens—immune complexes seen	Multiforme lesions of red urticaria, papules and target lesions on extremities, palms	Can involve mouth, eyes (Stevens-Johnson syndrome)
Cicatricial pemphigoid	Subepidermal IgG linear in basement membrane zone	Scarring blisters in the mucous membrane; 25% have blisters on skin	Causes blindness; stenosis of urethra, anal areas
Dermatitis herpetiformis (vesicles in dermal papillae)	Immunologic deposition of IgA in dermal papillae	Grouped, symmetrically distributed vesicles and urticarial papules on scalp, scapulae, buttocks, elbows, knees	Intense burning, itch; high incidence of asymptomatic celiac sprue
Metabolic			
Porphyria cutanea tarda	Metabolic defect in porphyrin metabolism	Tense bullae that leave scars in sun-exposed areas; bullae induced by sun, trauma	May also see facial hirsutism and hyperpigmentation
Bullous disease of renal disease	Unknown	Bullae usually on extremities	
Bullous disease in diabetics	Unknown	Large bulla on acral areas	
Mechanicobullous diseases			
Epidermolysis bullosa (split above, below, and within dermal-epidermal zone)	Variety of inherited conditions	Tense blisters that erode and scar, especially in recessively inherited forms; can lead to severe scars covering digits	Severe forms may involve mouth, esophagus
Epidermolysis bullosa acquisita (blister below lamina densa)	Linear IgG and C3 deposits below lamina densa	Tense blisters that lead to scars and milia in pressure and trauma sites on hands, feet; scarring mucous membrane lesions also occur	Circulating antibody to sublamina densa antigen found

slide and stained with Wright or Giemsa stain to reveal multinucleated giant cells (see Ch. 532).

Acyclovir administered orally and intravenously is the most frequently used form of therapy for primary and recurrent forms of herpes (see Ch. 340 and Fig. 532–4).

Varicella infection, when initially encountered, causes chickenpox, a generalized pruritic eruption with widespread, delicate vesicles on an erythematous base which have been likened to a dew drop on a rose petal. They often become umbilicated, hemorrhagic, and pustular and may leave scars. Chickenpox lesions occur predominantly on the trunk but also involve the head, extremities, and mucous membranes of the mouth and conjunctiva. Successive crops of lesions evolve for a week. *Herpes zoster* is a recrudescence of latent varicella virus in persons who previously had varicella. It appears as grouped, umbilicated, and, at times, hemorrhagic vesicles and pustules on an erythematous base situated unilaterally along the distribution of cranial or spinal nerves. Frequently several immediately adjacent dermatomes are involved. Bilateral involvement is rare. Zoster is frequently associated with a prodrome of severe radicular pain in the involved areas. A common useful sign in making the diagnosis is hypesthesia of the dermatomal areas—the patient often bitterly complains that the rubbing of clothing on the area is intolerable. Most patients with herpes zoster are over 50 years of age, and cancer patients (especially those with lymphomas such as Hodgkin's disease) are particularly prone to this infection. In such patients or in immunocompromised individuals, cutaneous dissemination from the original dermatome may occur, as well as visceral involvement of liver, lung, and central nervous system. Postherpetic neuralgia is common in individuals over 50. Treatment of herpes zoster is usually symptomatic with Burow's compresses, analgesics, and acyclovir, especially in immunocompromised patients.

Insect bites including flea and fire ant bites may also induce vesicles or bullae, a response to injected toxins or foreign chemicals or proteins in the bite or an allergic reaction to them.

Several unusual conditions, the *pemphigus diseases*, cause blistering in the epidermis by virtue of the process of acan-

and IgM with anti-IgG or rheumatoid factor activity), which may be idiopathic or occasionally associated with systemic lupus erythematosus, infectious mononucleosis, lymphomas, or primary biliary cirrhosis.

If the vasculitis is idiopathic and cutaneous, the skin responds to prednisone (60 to 80 mg per day) or dapsone (100 to 150 mg per day). Systemic vasculitides may require prednisone and cyclophosphamide (2 mg per kilogram per day).

Necrotizing cutaneous vasculitis may occur in association with *hepatitis B* and in patients with *intestinal bypass surgery* for morbid obesity or in patients with jejunal diverticula or other gastrointestinal conditions characterized by bacterial overgrowth. An *arthritis-dermatitis syndrome* with intestinal bypass surgery may occur with polyarthritis and palpable purpura or purpuric nodules and pustules on the trunk, legs, feet, and arms. Antigenic components of the intestinal bacterial overgrowth lead to the formation of cryoprotein immune complexes that deposit in the skin and joints, causing a hypersensitivity vasculitis and nondeforming arthritis. Antibiotics such as chloramphenicol, sulfamethoxazole-trimethoprim, tetracycline, and metronidazole have been reported to improve the condition.

PAPULOSQUAMOUS SKIN DISEASES

Unique scales are the common characteristic of diseases in this group. *Squamous* refers to scaling that represents thickened stratum corneum and thus implies an abnormal keratinization process. The lesions, in addition to being scaly, are characterized by sharply demarcated, red to violaceous papules and plaques that result from thickening of the epidermis and/or underlying dermal inflammation.

The papulosquamous disorders have diverse etiologies and include psoriasis, Reiter's syndrome, pityriasis rosea, lichen planus, pityriasis rubra pilaris, secondary syphilis, mycosis fungoides, and ichthyosiform eruptions (Table 534–4).

PSORIASIS. Psoriasis is a genetically determined, chronic epidermal proliferative disease of unpredictable course. Onset is most frequent in early adult life, but it may begin at any age. Once the disease becomes manifest, it may remain localized to a few areas or may cause intermittent or continuous generalized disease.

The lesions appear as erythematous papules and plaques surmounted by silvery, thick scales that resemble mica (micaceous) and that are easily removed and may accumulate in the patient's clothing or bed (Fig. 534–6). In intertriginous areas maceration prevents scales from accumulating, but the lesions remain red and sharply defined. Classically, lesions are distributed symmetrically over areas of bony prominence such as elbows and knees. They also commonly occur on the trunk and scalp and in the intergluteal cleft. These latter two areas are frequently overlooked. Palms and soles may be involved, with diffuse redness, scaling, and, at times, pustular lesions. Nail involvement occurs in up to 50 per cent of patients. The nails may be pitted with small ice pick–like depressions on the surface of the nail plate. Onycholysis can also occur, in which a plaque of psoriasis in the distal nail bed causes a red-brown discoloration that is reminiscent of an oil stain under the nail. Another helpful diagnostic feature is the Koebner phenomenon, in which intense trauma to the skin induces new skin lesions. Thus, scratches or surgical incisions elicit linear papulosquamous lesions that should alert the physician to the diagnosis. This may also explain the high incidence of psoriasis on the elbows and knees. Other aggravating factors include streptococcal infections, emotional

TABLE 534–4. PAPULOSQUAMOUS SKIN DISEASES

Disease	Appearance of Lesion	Distribution	Mucous Membrane Involvement	Other Features
Psoriasis	Erythematous plaques with silvery, mica-like scales, usually nonpruritic	Anywhere: scalp, knees, elbows, intergluteal cleft favored; symmetric	None	Koebner phenomenon, nail involvement, arthritis
Reiter's syndrome	Erythematous, silvery scaled plaques; hyperkeratotic papules of palms and soles (keratoderma blenorrhagica)	Similar to psoriasis	Frequent: mouth, genitals; balanitis circinata	Nail involvement, arthritis, urethritis, conjunctivitis, iritis
Pityriasis rosea	Tannish pink, oval papules and plaques with delicate collarette scale; may or may not be pruritic	Rash preceded by herald patch, Christmas tree pattern on trunk; spares face, extremities	None	May be associated with upper respiratory infection; drugs may cause similar rash
Secondary syphilis	Ham red or copper colored scaling papules and plaques, sometimes annular	Generalized: palms and soles often involved	Mucous patches, often white or red; condyloma warts of anal area	Condylomata in genital area; serologic test for syphilis positive
Lichen planus	Violaceous polygonal, flat-topped papules with white scale or Wickham's striae. May be hyperkeratotic, annular, or bullous lesions; pruritic	Often on wrists and ankles, but can be generalized; Koebner reaction	Frequent reticulated white patches or erosive lesions in mouth or genital areas	Occasionally involves nails; drugs can cause similar reaction
Pityriasis rubra pilaris	Red, scaling plaques and patches with follicular horny excretions, especially on dorsum of hands and fingers; diffuse, yellow hyperkeratoses of palms and soles	Often diffuse, rough scaling erythema involving entire body with islands of normal skin within scaling scalp	Occasionally lacy white plaques in mouth	Remits spontaneously in 2–4 years; nail changes as in psoriasis
Pityriasis lichenoides et varioliformis acuta (Mucha-Habermann disease)	Red, discrete, palpable papules that vesiculate and then become hemorrhagic, crust, scale, and leave a scar	Scattered lesions over trunk and extremities	May resemble leukocytoclastic vasculitis	May resolve in a few months or persist for years
Pityriasis lichenoides et varioliformis chronica (chronic parapsoriasis)	Guttate to larger, red slightly scaling papules and plaques; nonpruritic	Usually on trunk	Some forms may represent early stages of mycosis fungoides	Responds to UVB light treatments
Mycosis fungoides	Persistent, pruritic, red, thickened plaques with fine scales as seen in eczema, or thick mica-like scales suggestive of psoriasis; may ulcerate	Scattered asymmetrically over trunk, extremities; girdle area often first area involved	Neoplastic T-cell lymphoma	May show islands of normal skin within red areas
Ichthyosis	A variety of syndromes with variation in scaling skin; fine light scales to large, thick, coarse, verrucous scales that resemble fish skin; hyperkeratosis of palms and soles	Variable distribution but can involve flexural or extensor surfaces of extremities or trunk	Autosomal dominant, recessive, and X-linked recessive conditions	See Table 534–5

TABLE 534–9. CLINICAL FEATURES HELPFUL IN DISTINGUISHING BENIGN FROM MALIGNANT TUMORS

Clinical Feature	Benign	Malignant
Configuration	Symmetric, sharp borders	Asymmetric, irregular borders
Rate of growth	Slow	Slow or rapid
Friability	No friability	Often friable
Bleeding or ulceration	Seldom bleed or ulcerate	Often bleed and ulcerate
Consistency	Firm or soft	Usually firm to hard
Color	Uniform color and pigmentation	Irregularity of color and pigmentation

nign epidermal growths caused by papilloma viruses (see above, under Maculopapular lesions).

Sebaceous hyperplasia occurs as papular and occasionally nodular lesions on the faces of individuals past 50 years of age. This proliferation of sebaceous glands surrounding a hair follicle appears as groups of yellow papules evolving in an annular configuration with a central pore. Sebaceous hyperplasia is sometimes clinically difficult to differentiate from basal cell cancers, although the yellow discoloration and central pore may help. At times skin biopsy may be necessary. No treatment is generally required.

Keratoacanthomas, or self-healing epitheliomas, are rapidly

TABLE 534–10. NODULAR LESIONS OF THE SKIN

Lesion	Appearance	Distribution	Etiology	Other Factors
Nonpigmented Nodules—Benign				
Warts	Skin-colored, corrugated hyperkeratotic surface	Anywhere on body	Papillomavirus	Appearance may vary, depending on location of wart; i.e., plantar warts are flat with callus on surface; condylomata acuminata are soft, moist, cauliflower-like nodules
Sebaceous hyperplasia	Yellow, papular nodules, lesions	Face	Benign hyperplasia of sebaceous glands	
Keratoacanthoma	Rapidly growing nodule with keratin-filled central crater	Sun-exposed areas	Benign hyperplasia of keratinocytes	Resolves spontaneously leaving scars
Epidermal inclusion cyst	Flesh-colored, firm nodules with rubbery consistency and enlarged pore on surface	Often scalp, face, trunk	Epidermally lined cysts	Occasionally becomes secondarily infected
Lipoma	Multilobulated, firm nodule with normal overlying epidermis	Extremities, trunk	Benign localized hypertrophy of adipose tissue	
Neurofibroma	Soft, flesh-colored, protruding nodules that can be invaginated deeper into skin—buttonhole sign	Extremities, trunk	Hyperplasia of neural tissue in dermis	Can be associated with von Recklinghausen's disease and café au lait spots and axillary freckling
Nonpigmented Nodules—Malignant				
Basal cell carcinoma	Opalescent, waxy nodule often with ulceration	Sun-exposed areas, 97% face, neck, arms	Ultraviolet light and genetics play a role	Locally invasive—seldom metastasizes
Squamous cell cancer	Hard, smooth or verrucous nodules that often show hyperkeratinization	Sun-exposed areas	Ultraviolet light and genetics play a role	May be metastatic, especially those on lower lip
Pigmented Nodules—Benign				
Seborrheic keratosis	Light brown to black verrucous lesions with stuck-on appearance	Face, trunk	Seen in older people	Individual lesions of uniform color
Dermatofibroma	Firm dermal papules and nodules with overlying brown hyperpigmentation; dimple sign—dimpling of epidermis with pinching of skin	Usually legs	Trauma, insect bites induce dermal fibrosis	Can be flesh-colored or red
Nevi	Uniformly pigmented, flat to nodular symmetrically shaped lesions	Anywhere on body	Accumulation of benign pigmented nevus cells	Itching nevi or changes in color, size, or configuration are danger signs of melanoma
Pigmented Nodules—Malignant				
Melanoma	Flat to nodular, pigmented lesions with asymmetry of growth, irregular borders, variegation of pigmented, and diameter greater than 6 mm	Anywhere on body	Probably ultraviolet light exposure; genetic predisposition	Itching may be early sign of melanoma; melanoma can arise from pre-existing nevi
Vascular Tumors of Skin				
Hemangiomas	Flat to nodular, red, blue, purple, soft lesions	Anywhere on body	Proliferation of blood vessels of dermis	Strawberry hemangiomas usually regress; port-wine stains persist
Pyogenic granuloma	Bright red nodules that readily bleed	Extremities, hands, fingers	Proliferation of blood vessels following trauma	
Kaposi's sarcoma	Red, purple, brown papules and plaques	Legs, neck, trunk	Cytomegalovirus, AIDS	See most often with AIDS or immunosuppression
Inflammatory Nodules of Skin				
Erythema nodosum	Multiple, red, painful nodules; do not ulcerate; involute leaving bruises	Pretibial areas	Hypersensitivity reaction in subcutaneous fat	Number of antigenetic stimuli: drugs, infections, intestinal inflammatory disease
Subcutaneous fat necrosis	Red nodules, tender	Lower legs, thighs	Fat necrosis secondary to release of pancreatic lipase	Pancreatitis, pancreatic cancer
Rheumatoid nodules	Nonpainful, firm nodules	Elbows, knees, fingers	Unknown	Rheumatoid arthritic changes with high rheumatoid factor titer
Nodules Associated with Metabolic Conditions				
Xanthomas	Nontender, firm, yellow to red papules and nodules	Elbows, knees, Achilles tendons	Hyperlipoproteinemias	Xanthomas related to genetic disorders of lipoprotein metabolism (primary) or secondary to underlying diseases

tumors. Platelet consumption by large cavernous he-
iomas may occur in the *Kasabach-Merritt syndrome*. Or-
ily no therapy is required for hemangiomas; watchful
ng allows the lesions to resolve spontaneously, the
etic result usually being superior to that obtained by
peutic intervention.

genic granuloma, a bright red, raspberry-like growth that
each a centimeter in size, is friable and bleeds easily
traumatized. These lesions occur most often on arms,
fingers, and hands. They enlarge rapidly within weeks
ave no malignant potential; they represent capillary
ngiomatous proliferation and occur following injury or
ry. The term *pyogenic* is a misnomer, as no infectious
ss is involved. These lesions are treated with excision,
tage and electrocauterization, or cryotherapy.

posi's sarcoma is a rare neoplasm of multifocal origin which
nts as red-purple to blue-brown macules, plaques, and
les of the skin and other organs. The cutaneous lesions
be firm or compressible, solitary or numerous, and may
appear initially as a dusky stain, especially about the

ese round-cell and spindle-cell sarcomas are also found
scera and until their association with AIDS was recog-
l, seemed to occur predominantly in older men, leading
eir demise. In Europe and North America, where Kaposi's
oma is more frequently seen among Jews and those of
iterranean descent, the lesions commonly affect the lower
mities, are indolent, and often are associated with chronic
hedema, indicating tumor infiltration of the lymphatics.
are affected 10 to 15 times more often than women, are
lly in their seventh decade, and have an average survival
of approximately 10 years. The incidence of such Kaposi's
oma reported for the United States is less than 0.1 per
00 population and fewer than 0.02 per cent of all malig-
les.

tropical Africa, however, there is an endemic belt at an
ude of 1200 to 1500 meters where the disease accounts for
9 per cent of all malignancies, afflicting the black popu-
n while sparing white people and Indians. It has a peak
lence in the first decade, with most patients less than 20
s of age, and with survival of less than three years.
eral rather than cutaneous involvement and marked
phadenopathy are the predominant clinical signs in these
can children, who exhibit a unique form of Kaposi's
oma found in no other population.

ne selective geographic distribution of the lymphadeno-
ic type of Kaposi's sarcoma is remarkably similar to that
urkitt's lymphoma. With electron microscopic studies that
m an association between cytomegalovirus and Kaposi's
oma, another parallel is made with Burkitt's lymphoma,
malignancy so closely linked to the Epstein-Barr virus. In
acquiring of Kaposi's sarcoma, therefore, it would seem
infectious agents and immune status are of significance,
ell as genetic and environmental factors. Kaposi's sarcoma
been observed to complicate systemic lupus erythemato-
being treated with immunosuppression and to appear
ng with tumors of lymphoreticular origin in the immuno-
pressed recipients of renal transplants. It is known to
xist with other primary malignancies. However, its ap-
rance as an aggressive lethal tumor in the young male
nosexual is the stunning observation of grave concern.
se affected have a mean age in the fourth decade. Their
lesions are generalized in distribution and are smaller,
er, and lighter in color than the classic firm, indurated
ons of the legs. Mucous membrane tumors or symptomatic
eral or lung lesions may appear before the hemorrhagic
comas of the skin. Average survival time from onset of the
ease is less than two years.

uch fulminant Kaposi's sarcoma appears alone or with
umocystis carinii pneumonia and other opportunistic infec-
as in increasing numbers in male homosexuals and drug abusers. A small painless red nodule of the skin, easily overlooked, can signal a profoundly compromised immune state and grave prognosis (see Ch. 346 and Color plate 6*D*, *E*, and *F*).

INFLAMMATORY NODULES OF THE SKIN. *Erythema nodosum* is an inflammatory reaction in subcutaneous fat which represents a hypersensitivity response to a number of antigenic stimulae. These well-localized, multiple, tender, red, deep nodules, 1 to 5 cm in size, usually develop bilaterally over the pretibial areas. They eventually involute, leaving yellow-purple bruises. Ulceration does not occur. Immunoglobulin and complement deposition has been found in deep blood vessels in early lesions, and in some patients circulating immune complexes have been detected. The localization of the painful nodules to the lower legs may be related to hemodynamic factors. Although no cause can be found in many patients, the following etiologic factors have been identified: drugs, pregnancy, inflammatory bowel disease, sarcoidosis, streptococcal infection, *Yersinia* enterocolitis, deep fungus infections, and tuberculosis. If the etiology cannot be identified and eliminated, symptomatic therapy with aspirin, nonsteroidal anti-inflammatory medications, or occasionally short courses of systemic steroids may be useful.

Subcutaneous fat necrosis is a condition in which tender, red nodules occur on the lower legs and thighs in patients with pancreatitis or pancreatic carcinoma. The skin lesions may occur in the absence of signs associated with the internal carcinoma. Serum amylase and lipase values are elevated, and skin biopsy will provide diagnostic findings.

Rheumatoid nodules are subcutaneous inflammatory lesions usually found over elbows, knees, and fingers in patients with severe rheumatoid arthritis and high rheumatoid factor titer (see Ch. 433).

NODULES ASSOCIATED WITH METABOLIC DISEASES AND MISCELLANEOUS CONDITIONS. *Xanthomas* are focal collections of lipid-containing histiocytes in the dermis and tendon sheaths which appear as yellowish papules (eruptive xanthomas), plaques (xanthelasma), nodules (xanthoma tuberosum), and xanthomas in tendon and tendon sheaths (xanthoma tendinosum). Xanthomas often arise in association with inherited hyperlipoproteinemias (see Ch. 183) or in a variety of underlying metabolic diseases that alter lipoprotein metabolism, such as diabetes, hypothyroidism, cholestatic liver disease, pancreatitis, and renal disease, and in reaction to some drugs (e.g., 13-*cis*-retinoic acid). Xanthelasma usually develops in the absence of hyperlipidemia, although hypercholesterolemia (and increased low density lipoproteins) may be present.

Patients with gout occasionally deposit sodium urate in the skin, forming firm, hard papules and nodules (tophi) that may discharge whitish crystals in the pinnae of the ears and periarticular areas.

ATROPHIC SKIN CONDITIONS WITH SCARRING, INDURATION, ULCERATION, AND TELANGIECTASIAS

Connective tissue diseases are the most common conditions that lead to this spectrum of cutaneous changes.

SCARRING. *Lupus erythematosus* may be localized to the skin (discoid lupus) or present as a systemic condition (see Ch. 436) (Table 534–11). Discoid lupus skin lesions appear as red plaques with white, cohesive scales that often are accentuated in the follicular openings (follicular plugging). The plaques eventually atrophy, with depression and scarring along with hypopigmentation in the center of the lesions and a hyperpigmented rim. The lesions usually occur in sun-exposed areas and, when they involve the scalp, cause scarring alopecia. Systemic lupus erythematosus presents as an erythematous rash with a violaceous hue, accentuated in sun-exposed areas, especially the malar area, producing a butterfly configuration. Telangiectasias may also be prominent, and, at

TABLE 534–11. ATROPHIC SKIN CONDITIONS WITH SCARRING, INDURATION, ULCERATION, AND TELANGIECTASIAS

Condition	Etiology	Important Physical Findings	Other Facts of Note
Connective Tissue Diseases			
Discoid lupus	Autoimmune conditions	Plaques with atrophic centers, erythematous and telangiectatic borders; follicular plugging prominent	May rarely be associated with systemic LE
Systemic lupus	Unknown	Erythematous, scaling, telangiectatic rash in sun-exposed areas; butterfly configuration on face; periungual telangiectasias	Antinuclear antibodies plus arthritis and serositis
Dermatomyositis	Unknown	Heliotrope of eyelids; Gottron papules on knuckles, poikilodermatous changes on face, V of neck, elbows	Proximal muscle weakness; occasionally associated with underlying cancer
Morphea	Unknown	Localized patches of induration with erythematous borders	Seldom related to systemic sclerosis
Progressive systemic sclerosis	Unknown	Hidebound, indurated, tight skin over acral areas and face; periungual and matlike telangiectasias; ulcerations of fingertips	Raynaud's phenomenon common; lungs, heart, GI tract may also be involved
Lichen sclerosus et atrophicus	Unknown	Porcelain white, indurated plaques commonly on genitalia but may occur on trunk; follicular plugging may be seen	
Cutaneous Ulcers of Extremities			
Venous and arterial insufficiency	Impairment of vascular flow	Arterial insufficiency causes ulcers; gangrene acrally with associated claudication; venous ulcers usually around malleoli in association with stasis dermatitis	Lower leg and foot edema common in venous insufficiency
Hemoglobinopathies	Poor oxygenation of tissue	Sickle cell anemia and other hemoglobinopathies can cause ulcerations on lower third of leg	
Pyoderma gangrenosum	Hypersensitivity reaction	Deep, necrotic ulcer with undermined violaceous borders, usually on the legs	Associated with ulcerative colitis, rheumatoid arthritis, dysproteinemia
Ecthyma gangrenosum	*Pseudomonas* septicemia	Ulcers with erythematous borders, usually in body folds	Often early sign of *Pseudomonas* septicemia
Genital Ulcers			
Venereal diseases			
Herpes	*Herpes virus hominis*	Grouped vesicles that leave superficial erosions	VDRL may or may not be positive
Syphilis	*Treponema pallidum*	Superficial, indurated, painless ulcer	
Chancroid	*Haemophilus ducreyi*	Multiple, soft, painful ulcers with undermined edges	
Lymphogranuloma venereum	*Chlamydia trachomatis*	Transient, painless skin ulcer—inguinal bubo	
Granuloma inguinale	*Donovania granulomatis*	Nodules that erode with granulation tissue ulcer	
Behçet's disease	Autoimmune disease	Multiple shallow genital ulcers in association with oral aphthae and iritis	Erythema nodosum, arthritis, and CNS symptoms also seen

times, fine scaling is seen. Occasionally bullae, erosions, and ulcers also occur. Periungual telangiectasia is a prominent finding in systemic lupus as well as in other connective tissue diseases. Subacute lupus is a form in which psoriasiform skin patches are found on the face and trunk.

Dermatomyositis (see Ch. 443) findings include violaceous edema of eyelids (heliotrope), flat-topped papules over the knuckles (Gottron's papules), and reticulated patches of hyper- and hypopigmentation, erythema, and telangiectasia (poikiloderma) found on the V of the neck, face, elbows, and knees.

X-radiation can cause chronic skin changes of atrophy, telangiectasias, irregular pigmentation, and eventually ulceration. Within these areas malignant changes may later appear.

DERMAL INDURATIONS (SCLEROSIS). *Scleroderma* is a condition in which excessive collagen is found in the dermis (see Ch. 437). *Morphea* is localized scleroderma confined to the skin, whereas *systemic scleroderma*, or *progressive systemic sclerosis*, is a more extensive form in which fibrosis diffusely involves the skin as well as internal organs (see Ch. 437). Morphea lesions are asymptomatic, oval to irregular, whitish, firm, thickened patches with an erythematous border. The plaques are most often found on the trunk. The thickened skin in progressive systemic sclerosis is not sharply demarcated, but rather causes indurated, "hide-bound" tight skin over the fingers, toes, and extremities (acrosclerosis). Thickening of the facial skin causes smoothness and loss of wrinkles except for furrowing around the mouth. Ulcerations followed by pitted scars occur on the finger tips. Telangiectasia may be prominent, appearing as periungual telangiectasias and multiple, small punctate macules on the face and hands (matlike telangiectasia). A variant of systemic scleroderma, the *CREST syndrome*, displays extensive telangiectasias over face and hands. Patients with *hereditary hemorrhagic telangiectasia* also display telangiectasia, particularly around the mouth and nose and on the fingers as well as vascular malformations in the gastrointestinal tract and, at times, the lung. No cutaneous induration is found in this condition.

Lichen sclerosus et atrophicus may be confused with morphea, presenting as porcelain white, atrophic, indurated plaques most commonly on the vulva or on the male genitalia (balanitis xerotica obliterans). At times it occurs as scattered patches on the trunk.

Myxedema may cause a coughy thickening of the skin from deposition of glycosaminoglycans in the dermis. This may be localized to the pretibial areas (pretibial myxedema) as firm, nonpitting plaques and nodules with accentuation of the follicular orifices giving a peau d'orange appearance.

CUTANEOUS ULCERS. Primary skin ulcers are caused by a wide variety of etiologies and conditions. The location of the ulcers, the symptoms associated with them, and the rapidity of their appearance are important clues in diagnosing their various etiologies.

Ulcers of the extremities are frequently associated with vascular disease. Sudden pain associated with numbness of an extremity and ulceration suggest arterial occlusion. Ulceration of digits associated with a purplish red color with dependency and pallor when the extremity is elevated suggests arteriosclerotic peripheral vascular disease. Brawny edema, brown discoloration, and dermatitis over the lower legs in association with ulcers around the malleoli are seen with venous insufficiency. Sickle cell anemia causes ulcerations in the lower third of the leg. Areas of pressure and trauma, particularly on the foot, in patients with peripheral neuropathy, are susceptible to neurotrophic ulcers (mal perforant), as in diabetes and leprosy. The skin around the ulcer is anesthetic and callused. Pressure sores or decubitus ulcers occur in immobilized debilitated patients. Shearing forces, friction, moisture, and pressure contribute to the development of these sores. The sacral and coccygeal areas, ischial tuberosities, and greater trochanters are favored sites. The best treatment of pressure sores is prevention by frequently mov-

ing immobilized patients, keeping the skin clean, and using air mattresses.

An unusual and dramatic ulcerative condition, *pyoderma gangrenosum*, often begins as an inflammatory nodule or pustule resembling a furuncle which breaks down, ulcerates, and gradually enlarges peripherally. Fully developed, the lesions are moderately deep, red, necrotic ulcers with undermined, violaceous, edematous borders. These lesions, which typically evolve on the lower legs, are postulated to represent a Shwartzman-like hypersensitivity reaction to a number of underlying internal conditions, including chronic ulcerative colitis, regional ileitis, rheumatoid arthritis, dysproteinemias, and occasionally leukemia or lymphoma. In over one half of the cases no etiology is identified.

Ecthyma gangrenosum is characterized by ulcerative lesions, often in the body folds (anogenital and axillary areas), in immunosuppressed patients with *Pseudomonas* septicemia. The painless lesions begin as hemorrhagic bullous patches that become necrotic and ulcerate and are surrounded by considerable erythema with a central gray to black eschar. *Pseudomonas* can be cultured from these skin lesions.

Ulcerations on the genitalia are suggestive of venereal disease, including herpes simplex (multiple grouped vesicles and erosions), syphilis (indurated, painless, round ulcer with a clean base), chancroid (single or multiple, soft, painful, purulent ulcers with undermined erythematous edges), lymphogranuloma venereum (transient, painless skin ulcer with associated inguinal bubo-adenopathy), and granuloma inguinale (small nodules on genitalia which erode and become filled with velvety red granulation).

Multiple genital ulcers also occur in *Behçet's syndrome* in association with oral ulcers and ocular disease (iridocyclitis). Erythema nodosum, arthritis, and neurologic and intestinal involvement may also occur. The oral and genital ulcers are small, painful aphthae. Occasionally sterile pustules and ulcers at the site of minor trauma such as blood sampling can occur (pathergy) (see Ch. 433).

Geometric, bizarre-shaped, angular ulcers are characteristic of a self-inflicted, factitial cause.

HYPER- AND HYPOPIGMENTATION OF THE SKIN

Disorders of melanin pigmentation can be classified as hypomelanoses (decreased or absent epidermal melanin) or hypermelanoses (increased epidermal or dermal melanin). Hyper- and hypomelanosis can be further subdivided into localized or generalized (total body) alterations of pigmentation (Table 534–12).

Hyperpigmentary Conditions

LOCALIZED PIGMENTARY CONDITIONS. *Freckles* (ephelides) are light brown-red macules found in sun-exposed areas which are caused by increased melanin production in normal numbers of melanocytes. These occur in fair-complexioned individuals with red or sandy hair. Ultraviolet radiation increases melanin production in these lesions.

Lentigines are also hyperpigmented macules, but they occur because of increased numbers of melanocytes in the basal layer of the epidermis. Two types are recognized: (1) *lentigo simplex*, which occurs in early life and is congenital, and (2) *actinic lentigines*, which are acquired in middle age and are related to sun damage over the face, arms, and dorsum of the hands. Actinic lentigines are sometimes difficult to distinguish from early lentigo maligna on the face, but actinic lentigines have no malignant potential. The *multiple lentigines syndrome* is a rare, dominantly inherited condition character-

TABLE 534–12. HYPER- AND HYPOPIGMENTATION OF THE SKIN

	Etiology	Important Physical Findings	Other Facts of Note
Hyperpigmentation			
Localized			
Freckles	Increased melanin synthesis in skin	Light brown macules on sun-exposed areas	UV light accentuates
Lentigines	May be congenital or related to chronic sun exposure	Flat, light brown, uniformly pigmented lesions	No malignant potential
Melasma	Hormonal changes (pregnancy, birth control pills) plus sunlight	Irregular, flat, light brown areas on malar areas, cheeks, forehead	May fade after delivery or coming off birth control pills
Café au lait spots	Dominantly inherited pigmented lesion	Single to multiple coffee-with-cream–colored macules; may be associated with neurofibromatosis	Six or more such lesions suggest neurofibromatosis
Generalized			
Addison's disease	Increased MSH, ACTH	Diffuse hyperpigmentation with accentuation in body folds, palmar creases	Similar pigmentation with lung cancer; Cushing's disease with pituitary tumor
Hemochromatosis	Deposition of iron in skin and increased melanin in skin	Metallic gray-brown hyperpigmentation	
Chronic arsenic exposure	Stimulation of melanin synthesis in skin	Generalized hyperpigmentation studded with small depigmented macules	Keratosis on palms and soles
Hypopigmentation			
Localized			
Vitiligo	Immunologically mediated loss of melanocytes	Symmetrically distributed depigmented macules around body orifices and over bony prominences	In small percentage of cases associated with pernicious anemia, diabetes, thyroiditis
Piebaldism	Failure of melanocytes to migrate to skin in embryologic development	White forelock and depigmented patch—midline forehead, thorax	
Pityriasis alba	Dry skin	Pink, oval hypopigmented patches that often scale on face, trunk	Often accompanies atopic eczema, dry skin
Tuberous sclerosis	Dominantly inherited condition	Ash leaf–shaped, white macules on trunk, extremities; often present at birth	Associated with adenoma sebaceum, tuberous sclerosis
Generalized			
Oculocutaneous albinism	Autosomal recessive traits with variable degrees of tyrosinase insufficiency	White skin, hair; no pigment in fundi oculi; translucent irides	Nystagmus and eye problems common
Phenylketonuria	Deficiency of enzyme converting phenylalanine to tyrosine, so decreased precursor for melanin synthesis	Generalized depigmentation of hair, skin, eye color	Severe mental developmental defects if not diagnosed early and treated with special diet